REMARKS

Status of the claim

Claims 1, 2 and 4-8 are pending in the application, with claims 5 and 7 being withdrawn.

Rejection under 35 U.S.C.§103

Claims 1, 2, 4, 6 and 8 are newly rejected under 35 U.S.C.§103 as being obvious over JP '656 combined with US '956 and US '676. JP '656 is asserted to teach the use of a composition having hyaluronic acid of a molecular weight fraction of 10-60kDa, retinol acetate and vitamin A oil, for treating skin roughness. The composition of JP '656 is asserted to differ from the composition used in the instantly claimed method with regard to the recited fraction of hyaluronate of the instant claims. The composition of JP '656 is further asserted to differ in the use of retinol, whereas the instant claims recite the use of retinal. The secondary references of US '956 and US '676 are asserted to teach the hyaluronate fraction used in the instantly claimed method. US '956 is further asserted to teach a functional equivalence of retinol and retinal.

Claims 1, 2, 4, 6 and 8 remain rejected under 35 U.S.C.§103 as being obvious over US '956 combined with US '676. US '956 is asserted to teach topical compositions with retinoids, including retinal, for treating wrinkles and dryness of skin. US '956 is further asserted to teach the use of hyaluronic acid in the composition as a moisturizer. US '956 is asserted to differ from the instant claims in the molecular weight of the hyaluronic acid used in the composition. US '676 is relied upon for teaching moisturizing skin compositions with hyaluronate fractions having molecular weights of 10-200KDa and 1-4.5 million Da. US '676 is further asserted to teach that the hyaluronate having the lower molecular weight penetrates deeper into the tissue. The Examiner asserts that it would be obvious to one skilled in the art to replace the hyaluranate used in the composition of US '956 with that of US '676, to thereby obtain the instant invention.

With regard to the Declaration submitted on May 10, 2011, under 37 C.F.R.§1.132, the Examiner asserts the following. The Examiner finds the Declaration of Dr. SAURAT insufficient for the following reasons.

1) The Examiner asserts that the data in the Barnes et al. article, which was submitted with the Declaration, is not commensurate in scope with the claims because the claims recite hyaluronic acid fractions of 50,000 to 750,000; 50,000 to 250,000 and 250,000 to 750,000 daltons, whereas the experiments in Barnes et al. use a fraction of 50,000 to 400,000 daltons. The Examiner notes that while the assertion is made that the claimed fractions would be expected to exhibit similar activity, no evidence is provided in support of this assertion.

2) The Examiner also raises an issue based on the fact that the data in Barnes et al. is only based on mouse studies. The Examiner asserts that the claims must be therefore limited to mice.

3) Finally, the Examiner asserts that the results are not synergistic. The Examiner is relying on the fact that the results with RAL + HAF in Figure 1 of Barnes et al. appear to be what would be expected if the two separate activities are "added" together. Thus, the RAL + HAF appears "additive".

Applicants traverse these rejections and withdrawal thereof is respectfully requested. The invention, as encompassed by claim 1, is drawn to topical compositions, comprising as an active ingredient, one or more hyaluronate fragments, wherein the hyaluronate fragments all have a molecular weight of between 50,000 and 750,000 Da and retinal.

Attached hereto is a Declaration of co-inventor Dr. Gürkan KAYA, submitted under 37 C.F.R.§1.132. (A signed copy of the Declaration will be submitted upon receipt from Dr. KAYA.) The Declaration of Dr. KAYA demonstrates the unexpected improved properties associated with the invention and addresses the alleged deficiencies of the previously submitted Declaration of Dr. SAURAT.

As noted above, the Examiner asserts that the data in the Barnes et al. article is not commensurate in scope with the claims because the claims recite hyaluronic acid fractions of 50,000 to 750,000; 50,000 to 250,000 and 250,000 to 750,000 daltons, whereas the experiments in Barnes et al. use a fraction of 50,000 to 400,000 daltons. In the experiments presented in the Declaration of Dr. KAYA, a preparation of hyaluronate fragments having a molecular weight of 50-750 kDa (HAFi) was compared to preparations of fragments having a molecular weight of 30-50 kDa (HA 30-50) or 1000-1250 kDa (HA 1000-1250), in the presence or in the absence of

retinal (RAL). As shown in Figure 1 and as stated in the Declaration, hyaluronate fragments of 50-750 kDa (HAFi) significantly increase the production of hyaluronate (HA) by keratinocytes. Small (30-50 kDa) or high (1000-1250 kDa) molecular weight HAF did not induce HA production when compared with the control keratinocytes. The effect of HAFi fraction was potentiated by the retinaldehyde (RAL). Thus, as asserted previously, the activity observed with 50,000 to 400,000 daltons in the Barnes et al. article, is also observed with the claimed fractions.

The Examiner further asserted that because the data in Barnes et al. is allegedly only based on mouse studies the claims must be therefore limited to mice. However, the Examiner has given no scientific basis for why the sufficiency of the mouse model of Barnes et al. as being predictive of human activity is questioned. As the Court of Appeals for the Federal Circuit stated in *In re Brana*, 34 USPQ2d 1436 (Fed. Cir. 1995), animal models are perfectly acceptable to establish utility and acceptable *in vitro* testing can be used to establish enablement. Thus, the court has held that reliance on animal studies by Applicants to show the patentability of an invention, does not mean that the invention must be limited to that animal species. In addition, despite the adequacy of the animal testing it is further noted that human testing was done in both Barnes et al. (see e.g. final paragraph of page 4 before "Materials and Methods"; the paragraph bridging pages 5-6; the end of page 6; Figure 5, page 7) and Kaya et al., submitted with the Declaration of Dr. KAYA. Both Kaya et al. and Barnes et al. evidence the effect of the HAFi fraction on the human skin and its potentiation by RAL. Dr. KAYA further states that since the in vitro effects of the fractions of 50-400 kDa and 50-750 kDa on HA production by keratinocytes are very similar, the in vivo effects in humans would be expected by one skilled in the art to also be the same.

Finally, the Examiner had raised an issue with regard to the results of Declaration of Dr. SAURAT, noting that the results appeared to be additive and not synergistic. Applicants note that the test for supporting unobviousness is whether the invention possesses an unexpected properties. Not necessarily that the property be synergistic. See MPEP 2145. The Examiner's interpretation of the data is based on the fact the results with RAL + HAF appear to be would be expected if the two separate activities are "added" together. However, it is also readily apparent from the data that with the other samples of a retinoid and HAF, e.g. ROL + HAF, the activity appears to be no higher than with HAF alone, despite the fact that ROL alone also has an

activity. Thus, regardless of whether the RAL + HAF activity is defined as being "additive" and not "synergistic", the data shows that RAL + HAF has a statistically significant improved and unexpected activity when compared to HAF + other retinoids. Thus RAL + HAF possess unexpected properties.

In addition, a full consideration of all of the data disclosed in Barnes et al. as dicussed in the Declaration of Dr. KAYA, shows that the Examiner's conclusion is incorrect. Figure 5A of Barnes et al. shows western blot analysis performed on the protein extracts of mouse skin and demonstrates that the effect of HAFi and RAL on the protein expression of pro-HB-EGF was not additive but was synergistic (Barnes et al. (PLoS ONE 5(12): e14372, 2010).

Thus, the data of the Declarations of Dr. SAURAT and Dr. KAYA, as well as the journal articles of Barnes et al. and Kaya et al. demonstrate the unexpected properties associated with the instant invention. Withdrawal of the rejections is therefore respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact MaryAnne Armstrong, PhD, Registration No. 40069, at the telephone number of the undersigned below to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Director is hereby authorized in this, concurrent, and future replies to charge any fees required during the pendency of the above-identified application or credit any overpayment to Deposit Account No. 02-2448.

Dated: January 23, 2012

Respectfully submitted,

By _____
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Attachment: Declaration of Dr. KAYA